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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/678,554	10/04/2000	Annette Marian Doherty	5604-D1-01-TMC	1962

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Warner-Lambert Company
2800 Plymouth Road
Ann Arbor, MI 48105

EXAMINER
LUKTON, DAVID

ART UNIT	PAPER NUMBER
1653	

DATE MAILED: 10/01/2002

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	09/678,554	DOHERTY ET AL.	
	Examiner	Art Unit	
	David Lukton	1653	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).
- Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *03 April 2002* .

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-25* is/are pending in the application.

4a) Of the above claim(s) *15-18 and 20-23* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-14, 19, 24- 25* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

11)☐ The proposed drawing correction filed on _____ is: a)☐ approved b)☐ disapproved by the Examiner.

If approved, corrected drawings are required in reply to this Office action.

12)☐ The oath or declaration is objected to by the Examiner.

Priority under 35 U.S.C. §§ 119 and 120

13)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____ .

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

14)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. § 119(e) (to a provisional application).

a) ☐ The translation of the foreign language provisional application has been received.

15)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. §§ 120 and/or 121.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO-1449) Paper No(s) _____ .
4) ☐ Interview Summary (PTO-413) Paper No(s). _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: .

Paper No. 10 (filed 4/3/02) has directed (a) that claims 7, 8, 13, 24 and 25 be deleted, and (b) that claims 1-6, 9-12, 14 and 19 be amended. In addition, a copy of claims 1-12 has been provided in paper No. 10, and a "marked-up" copy has been provided for claims 13-24. However, these "marked-up" claims do not correspond to the previous claims, and as indicated, there is a directive to delete two of the claims which are supposed to be amended. Thus, there are numerous errors in the proposed amendment, and accordingly, the amendment has not been entered, with the exception of the abstract. All previously imposed rejections are maintained at this time. It is suggested that applicants resubmit an amendment which incorporates whatever changes are deemed appropriate, and which amendment includes a "clean copy" of amended claims, and a "marked-up" copy of the amended claims (no change in the abstract is needed). Of course, no claim should be amended and canceled at the same time.

Only the §112, first paragraph rejection is addressed at this time. The remaining rejections are merely maintained without further comment. After another amendment is submitted which makes applicants' intentions clear, the remaining issues will be addressed. Claims 15-18, 20-23 remain withdrawn from consideration at this time. Claims 1-14, 19, 24- 25 are examined in this Office action.

*

Claims 1-6 are rejected under the judicially created doctrine of obviousness-type double patenting as being unpatentable over claim 1 of USP 6,265,382; claim 19 (instant application) is rejected over claim 13 of '382. Although the conflicting claims are not identical, they are not patentably distinct from each other.

*

The following is a quotation of the first paragraph of 35 U.S.C. §112:

The specification shall contain a written description of the invention, and of the manner and process of making and using it in such full, clear, concise and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claims 19 and 25 are rejected under 35 U.S.C. 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to enable one skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention.

As indicated previously, applicants have shown (pp. 52-56) that the compounds of examples 1-8 exhibit some propensity to inhibit ras farnesyl transferase *in vitro*. However, this is not sufficient to enable the therapeutic method claims, or claims drawn to pharmaceutical compositions.

In response to the foregoing, applicants have pointed to Eskens (*Journal of Clinical Oncology* **19** (4) 1167-75, 2001), which states that the FT inhibitor SCH 66336 can be administered to humans. However, the reference makes no assertions about efficacy.

Next, applicants have pointed to Sharma (*Oncologist* **5** (2) 99-107, 2000), which quotes another scientist (Liu, 1998) as asserting some *in vivo* efficacy of in nude mice. Sharma also quotes another scientist (Skrzat, S.) as asserting that R115777 inhibited growth of human tumor xenographs of colon cancer in unspecified animals. No further information is given. Perhaps R115777 caused actual reduction of tumor volumes. Or perhaps R115777 was only cytostatic, and the animals died anyway. Or perhaps results were obtained which appeared on the surface to indicate efficacy, but the results were not statistically significant. Finally, applicants have pointed to Tolcher (*Oncologist* **6 Suppl 3** 40-4, 2001) who conveys that a few FT inhibitors are the subject of clinical trials. However, there is no conclusive evidence of efficacy.

The following references discuss the matter of various attempts by oncologists to treat cancer: Viallet (*Lung Cancer* **15** (3) 367-73, 1996); Kemeny (*Seminars in Oncology* **21** (4 Suppl 7) 67-75, 1994); Newton (*Expert Opinion on Investigational Drugs* **9** (12) 2815-29, 2000); Giese (*Journal of Cancer Research and Clinical Oncology* **127** (4) 217-25, 2001); Garattini (*European Journal of Cancer* **37** Suppl 8 S128-47, 2001); Ragnhammar (*Acta Oncologica* **40** (2-3) 282-308, 2001). As is evident, attempts to treat cancer using agents which have exhibited *in vitro* activity leads to "unpredictable" results. With respect to farnesyltransferase specifically, consider the following:

- Moasser (*Breast Cancer Research and Treatment* **73** (2) 135-44, 2002) discloses (e.g., abstract) that FT inhibitor sensitivity does not correlate with the relative

expression of Ras isoforms or the inhibition of Ras processing, growth factor signaling, expression of estrogen receptor or the overexpression of growth factor receptors. Also stated (last paragraph) is that Ras is not a molecular marker to guide FT inhibition therapy. This reference does not support the proposition that attempts to treat cancer patients will necessarily result in failure. However, it does support the proposition that there may be many forms of cancer which will be resistant to the effects of FT inhibition.

- Jiang (*Molecular and Cellular Biology* **20** (1) 139-48, 2000) discloses that while AKT2- transformed NIH 3T3 cells are sensitive to FTI-277, but that *ras*-transformed NIH 3T3 cells are not. This supports the proposition that one cannot predict which cells will be sensitive to FT inhibitors.

- Prendergast (*Molecular and Cellular Biology* **14** (6) 4193-202, 1994) discloses that the FT inhibitor L-739,749 inhibited growth of ras-transformed fibroblasts. However, L-739,749 had no effect on the growth, morphology, or actin organization of v-*raf*-transformed cells. This supports the proposition that one cannot predict which cells will be sensitive to FT inhibitors.

- Njoroge (*J. Med. Chem.* 40 (26) 4290-301, 1997) discloses that the Ras farnesyl-protein transferase inhibitor SCH 44342 did not show appreciable *in vivo* antitumor activity. This supports the proposition that *in vitro* activity is not necessarily predictive of therapeutic efficacy.

- Lerner (*Oncogene* **15** (11) 1283-8, 1997) discloses that the Ftase inhibitor FTI-277 is highly effective at blocking oncogenic H-Ras but not K-Ras4B processing and signaling. The results obtained demonstrate that while FTI-277 inhibits N-Ras and H-Ras processing in the human tumor cell lines evaluated, inhibition of K-Ras processing requires both an FTase inhibitor and a GGTase I inhibitor.

- Whyte (*J Biol Chem* **272**, 14459, 1997) discloses that geranylgeranyl transferase-1 is structurally related to farnesyl transferase, and that geranylgeranyl transferase-1 may alternatively prenyl K-Ras, thereby bypassing the effect of FPTase inhibition.

- Sharma (*Annals of Oncology* **13** (7) 1067-71, 2002) discloses results of a phase II trial of SCH 66336, an FPTase inhibitor, in patients with metastatic colorectal cancer. No objective responses were observed. It is concluded that future development of this compound cannot be recommended as monotherapy in this

disease.

Thus, attempts to treat cancer lead, in general, to "unpredictable" results, and [redacted] conclusive evidence of efficacy of Ftase inhibitors in humans is lacking. And even if it turns out that there is one example of a compound which inhibits Ftase, and which shows promise in humans who are stricken with a certain form of cancer, it remains to be determined which other forms of cancer will be susceptible to the Ftase inhibitors. And even if it turns out that there is one example of a compound which inhibits Ftase, and which shows promise in humans who are stricken with a certain form of cancer, the fact will remain that the degree of inhibition varies from one compound to the next, and applicants have not determined what degree of inhibition is necessary or sufficient. Then there are the issues of bioavailability and pharmacokinetics; these parameters will vary from one compound to the next. Where cancer chemotherapy is concerned, structure/activity relationships are "unpredictable", whether Ftase is involved or not; according, "undue experimentation" would be required to determined which compounds (if any) will be effective, and against which forms of cancer, and under what conditions. It is suggested that applicants claim either or both of the following, and to delete the term "pharmaceutical" at each occurrence:

> *A method of inhibiting ras farnesyl transferase in a mammal in need thereof comprising administering to said mammal a compound of claim 1 for a time and under conditions effective to inhibit ras farnesyl transferase.*

A method of inhibiting ras farnesyl transferase in a mammal afflicted with restenosis, cancer or psoriasis comprising administering to said mammal a compound of claim 1 for a time and under conditions effective to inhibit ras farnesyl transferase.

*

Claims 1-19, 19, 24-25 are rejected under 35 U.S.C. §112 second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

- Claim 1 is drawn to "compounds" in the plural. However, applicants are claiming single compounds, rather than mixtures of compounds. Accordingly, the term "compound" should be used in the singular. Moreover, the dependent claims recite "compound" in the singular. (To reiterate, the amendment of claim 1 has not been entered).

- The dependent claims recite "a compound". However, the definite article ("the") should be used instead, since the compounds that are referred to have already been identified.

- Claim 1 recites (last two lines):
  "and the pharmaceutically acceptable salts and prodrugs thereof".
  Thus, the question arises, are applicans claiming a mixture of compounds, salts of compounds and prodrugs of compounds? If so, the claim should be directed to a *mixture*. Otherwise, clarity would be enhanced by claiming *a compound* (in the singular) and reciting the following in the last two lines of the claim:
  ...or a pharmaceutically acceptable salt thereof, or a prodrug thereof.

- Claim 19 makes reference to a composition. However, a composition must have two components. Either or both of the following is suggested:
  A composition comprising a compound according to claim 1, and a carrier.

  A composition comprising a suitable carrier, and a compound according to claim 1 in an amount effective to inhibit ras farnesyl transferase.

- Claim 25 recites (last two lines): "for use a pharmaceutical". However, this renders the claim indefinite as to the objectives of the "pharmaceutical". For example, could the composition be used to treat multiple sclerosis, AIDS or Alzheimer's Disease?

*

The following is a quotation of the appropriate paragraphs of 35 U.S.C §102 that form the basis for the rejections under this section made in this action.

A person shall be entitled to a patent unless -

> (e) the invention was described in a patent granted on an application for patent by another filed in the United States before the invention thereof by the applicant for patent, or on an international application by another who has fulfilled the requirements of paragraphs (1), (2) and (4) of section 371(c) of this title before the invention thereof by the applicant for the patent.

Claims 1, 2, 5, 7, 19 are rejected under 35 U.S.C. §102(e) as being anticipated by Bolton (USP 5,830,868).

Bolton discloses (col 19) compound # 26. This corresponds to applicants variables as follows:

Y = oxygen

R3 = substituted benzyl

R2 = $-CH_2-CH_2-C_6H_5$

Thus, the claims are anticipated.

No claim is allowed.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to David Lukton whose telephone number is 703-308-3213. The examiner can normally be reached Monday-Friday from 9:30 to 6:00.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Christopher Low, can be reached at (703) 308-2923. The fax number for the organization where this application or proceeding is assigned is 703-872-9306.

Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to the receptionist whose telephone number is 703-308-0196.

DAVID LUKTON
PATENT EXAMINER
GROUP 1800